REMARKS

A. Summary of the Invention

Broadly, in one aspect, the subject invention relates to a method for determining the genotype at a genetic locus within genetic material obtained from a biological sample. The method comprises a step of reacting the material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus. A data set is formed which includes at least the first reaction value. The method of the invention further comprises a step of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of the invention also includes a step of applying the first reaction value to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. Finally, the method of the invention comprises a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution to determine a measure of the conditional probability of each genotype of interest at the locus.

B. Summary of the Outstanding Office Action

In the Office Action of 18 December 2003, claims 96 through 105 inclusive were finally rejected under 35 U.S.C. § 112, second paragraph, with the assertion that the claims were indefinite for assertedly failing to particularly point out and distinctly claim the subject matter which the applicant regarded as the invention. It was asserted that the expression "genotypic class identifier" recited in claim 96 was vague and indefinite.

Claims 96 through 105 inclusive were rejected under 35 U.S.C. § 112, first paragraph, in the outstanding Office Action with the assertion that the claims did not comply with the

written description requirement. It was asserted that there was no support in the specification for the term "identifier."

In the Office Action of 18 December 2003, claims 51 through 54 inclusive and 69 through 74 inclusive were finally rejected under 35 USC § 102(b) as unpatentable over a publication by Kimpton *et al.* in *PCR Methods and Applications*, volume 3, pages 13 through 22 (August 1993) ("the Kimpton *et al.* publication"). It was asserted that the Kimpton *et al.* publication disclosed at page 14 a method of determining the genotype at a locus within genetic material obtained by polymerase chain reaction ("PCR") amplification. With citations to pages 14 through 16 and Figures 1 and 2 of the Kimpton *et al.* publication, it was asserted that the method of the publication included (a) assembling reaction value data points for samples where each reaction value data point corresponded to a respective one of the samples and included at least one reaction value. It was asserted that the datapoints were represented by each of the separate peaks shown in Figure 1 of the publication and represented a different sample and that the datapoints were assembled as shown in Figure 2. It was asserted further that the method of the Kimpton *et al.* publication included a step (b) of determining an initial conditional probability for each reaction value data point for each genotype. It was asserted that the data was initially analyzed by analyzing bands to establish a conditional probability for reaction value, with a citation to page 15 and Figure 1. It was asserted further in the outstanding Office Action that the method of the Kimpton *et al.* publication included a step (c) of computing a conditional probability of each genotype for each reaction value data point. It was asserted that a calculation of band sizing determined the allele to which the sample belonged, assertedly thereby determining a genotype since assertedly a genotype was composed of particular alleles at particular positions. Page 16, columns 2 and 3 and page 17, Table 2 were cited in connection with this assertion. It was asserted further that the method of the Kimpton *et al.* publication comprised a step (d) of determining the genotype and confidence score for each reaction value data point, assertedly

thereby determining the genotype and confidence score at the genetic locus for each sample. Table 2 on page 17 was asserted to provide for each reaction point the genotype and a standard deviation based on the data obtained from step (d).

It was asserted further in the Office Action of 18 December 2003 that the Kimpton *et al.* publication disclosed reacting material at multiple loci and disclosed multiple alleles in probability distributions, with a citation to Tables 1 and 2 of the publication. Figure 2 on page 16 was cited in connection with an assertion that the Kimpton *et al.* publication disclosed the use of multiple data points derived from multiple runs of an automated apparatus, assertedly including multiple data sets, in the method and apparatus of the publication. It was asserted that the Kimpton *et al.* publication disclosed that the locus may be dinucleotide or tetranucleotide repeats and that the publication selected the loci for their discrimination ability and disclosed that several different loci may be analyzed.

In the outstanding Office Action, claims 51 through 54 inclusive and 60 through 74 inclusive were finally rejected under 35 USC § 103(a) as unpatentable over the Kimpton *et al.* publication in view of a publication by Clark in *Mol. Biol. Evol.*, volume 7, pages 111 through 122 (March 1990) ("The Clark publication"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication did not disclose modification of data to iteratively improve an assay. It was asserted that the Clark publication disclosed a method of resolving ambiguities by performing an iterative cascade of improvements on data points. It was asserted that the method of the Clark *et al.* publication was applied to restriction site polymorphisms. With a reference to a passage in the abstract of the Clark publication which asserted that the algorithm of the publication applied to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms, it was asserted that an ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of the Clark publication in the genotyping method of the Kimpton *et al.* publication

in order to extract as close to the entirety of the allelic sequences as possible. It was asserted further that an ordinary practitioner would have recognized that the method could be performed using any length marker, including single nucleotide polymorphisms such as the restriction site polymorphisms assertedly disclosed in the Clark publication.

Claims 51 through 54 inclusive and 56 through 74 inclusive were finally rejected under 35 USC § 103(a) in the Office Action of 18 December 2003 as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of published International Patent Application WO 92/15712 to Goelet *et al.* ("the Goelet *et al.* '712 published international application"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication even in view of the Clark publication did not teach genetic bit analysis, which was asserted to include allele specific amplification. It was asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of genetic bit analysis or allele specific amplification to develop the data in view of the Goelet *et al.* '712 international published application. It was asserted that an ordinary practitioner would have been motivated to substitute an assertedly equivalent genetic bit analysis method for PCR assertedly in order to minimize the need for gel electrophoresis and enhance the automatability of the process as assertedly motivated by the Goelet *et al.* international published application assertedly in order to speed analysis and minimize cost.

Claims 51 through 54 inclusive, 56, 58, and 60 through 74 inclusive were finally rejected in the outstanding Office Action under 35 USC § 103(a) as unpatentable under the Kimpton *et al.* publication in view of the Clark publication and further in view of United States patent No. 5,516,663 to Backman *et al.* ("the Backman *et al.* '663 patent"). It was admitted in the Office Action that the Kimpton *et al.* publication even in view of the Clark *et*

al. publication did not disclose the use of a ligation chain reaction. It was asserted that the Backman *et al.* '633 patent disclosed a method of ligation chain reaction. It was asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of a ligation chain reaction as assertedly disclosed in the Backman *et al.* '663 patent. A passage at column 2, lines 8 through 10 of the Backman *et al.* '663 patent was cited in this connection. It was asserted that an ordinary practitioner would have been motivated to substitute the ligation chain reaction for an assertedly equivalent amplification method of polymerase chain reaction with the asserted motivation that the ligation chain reaction assertedly could detect small numbers of target molecules and assertedly because ligation chain reaction was a known equivalent amplification assay to the polymerase chain reaction disclosed in the Kimpton *et al.* publication.

In Section 8 of the Office Action of 18 December 2003, claims 75 through 83 inclusive, 85, 86, 88, 89, 91 through 93 inclusive, 95, 96 through 99 inclusive, and 103 through 105 inclusive were finally rejected under 35 U.S.C. §103(a) as unpatentable over the Kimpton *et al.* publication in view of a publication by Ledwina *et al.* in *Biometrics,* volume 36, pages 160 through 165 (1980) ("the Ledwina *et al.* publication") and further as motivated in view of a publication by Jeanpierre in the *Annals of Human Genetics*, volume 56, page 325 through 330 (1992). ("the Jeanpierre publication") It was asserted that the Kimpton *et al.* publication disclosed at page 14 a method of determining the genotype at a locus within genetic material obtained by PCR amplification. With citations to page 14, columns 1 through 3 of the Kimpton *et al.* publication, it was asserted that a method of the publication included reacting material at the locus to produce a first reaction value. It was asserted further, with a citation to pages 14 through 16 of the Kimpton *et al.* publication, that the publication disclosed forming a data set including the first reaction value by assembling reaction value

data points for samples with each reaction value data point assertedly corresponding to a respective one of the samples and including at least one reaction value. It was asserted that the data points represented by each of the separate peaks in Figure 1 represented a different sample and were assembled in Figure 2. With a reference to pages 16 and 17 of the Kimpton *et al.* publication, it was asserted that the Kimpton et al. publication disclosed determining the genotype and a confidence score for each reaction value data point assertedly to determine the genotype and confidence score at the genetic locus for each sample. It was asserted that Table 2 on page 17 of the publication provided for each reaction point the genotype and a standard deviation based on the data obtained from a step D. With regard to claims 77 and 78, it was asserted that the Kimpton et al. publication disclosed reacting the material at multiple loci at page 14, Table 1. With regard to claims 80 through 82, it was asserted that the Kimpton *et al.* publication on page 17 considered multiple alleles in the probability distributions. Table 2 was cited with the assertion that the Table disclosed that the method was applicable to any number of alleles. It was asserted that Kimpton expressly disclosed the use of multiple data points derived from multiple runs of an automated apparatus including multiple data sets in the method and apparatus disclosed at page 16 and in Figure 2.

Significantly, it was admitted in the outstanding Office Action that, although the Kimpton *et al.* publication disclosed the use of a Hardy-Weinberg test, the publication did not disclose establishing a distribution set of probability distributions and did not disclose applying the reaction value of the distributions to determine a measure of the conditional probability of each genotype of interest at the locus.

It was asserted in the Office Action of 18 December 2003 that the Ledwina *et al.* publication disclosed a method in which genotypes could be determined in which the Hardy-Weinberg test was modified assertedly to include the steps of establishing a distribution set of probability distributions and associating hypothetical values with corresponding

probabilities for each genotype of interest. Pages 162 and 163 of the Ledwina *et al.* publication were cited in this regard. It was asserted further that the Ledwina *et al.* publication disclosed the step of applying the first value to each pertinent probability distribution to determine a measure of conditional probabilities of each genotype of interest, citing in particular pages 162 and 163 of the Ledwina *et al.* publication. It was asserted further in the Office Action that, with respect to claims 76 and 79, the Ledwina *et al.* publication, in referring on page 162 to "common probability distribution of (T,Z) is multinomial with ½m(m+1) cells and with the vector of cell probabilities g=(g...)," assertedly disclosed a plurality of distributions which were hypothetical. It was asserted that the Jeanpierre publication motivated the use of computation of unknown genotypes to analyze conditional probabilities relative to a distribution of hypothetical reaction values. Page 330 of the Jeanpierre publication was cited in this connection.

It was asserted in the outstanding Office Action that it would have been prima-facie obvious to one of ordinary skill in the art the time the invention was made to modify the method of the Kimpton *et al.* publication to use a conditional probability distribution method assertedly disclosed in the Ledwina *et al.* publication, since the Kimpton *et al.* publication assertedly noted that the analysis of the publication used Hardy-Weinberg equilibria and since the Ledwina *et al.* publication disclosed a class of admissible tests for the Hardy-Weinberg equilibrium in a multiple allelic system. It was asserted that an ordinary practitioner would have been motivated to apply the asserted hypothetical distribution analysis to genotyping since the Jeanpierre publication assertedly disclosed certain gains from creating such a distribution, including avoiding a hazard of incorrectly using a simple average of conditional probabilities instead of a harmonic means.

In Section 9 of the Office Action of 18 December 2003, claims 75 through 86 inclusive, 88, 89, 91 through 93 inclusive, 95, 96 through 99 inclusive, and 103 through 105

inclusive were finally rejected under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre publication, the same publications as cited in the preceding Section 8. It was asserted that the hypothetical combination of the Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated in view of the Jeanpierre publication disclosed the limitations of claims 75 through 83 inclusive, 85, 86, 88, 89, 91 through 93 inclusive, and 95. It was admitted in the Office Action that the hypothetical combination of the Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated by Jeanpierre did not disclose iteration of the method. It was asserted that the Clark publication, which was not specifically identified in the rejection of the claims set out in the first sentence of Section 9, disclosed a method of resolving ambiguities by performing an iterative cascade of improvements on data points. It was asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the iterative screening and improvement methods of the Clark publication with the probability method of Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated by the Jeanpierre publication in view of a statement in the Clark publication concerning an algorithm for extracting allelic sequences applied to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms. It was asserted that an ordinary practitioner would have been motivated to apply the idea of iterative data processing of the Clark publication in the genotyping method of the hypothetical combination of the Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated by the Jeanpierre publication in order to extract as close to the entirety of the allelic sequences as possible.

Claims 75 through 83 inclusive, 85 through 95 inclusive, 96 through 101 inclusive, and 103 through 105 inclusive were rejected under 35 U.S.C. § 103(a) in Section 10 of the outstanding Office Action over the hypothetical combination of the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as motivated in view of the Jeanpierre

publication, the same three publications as cited in the preceding Sections 8 and 9. It was admitted that the hypothetical combination of the Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated by the Jeanpierre publication did not teach genetic bit analysis which assertedly included allele specific amplification, nor the particular alleles listed. It was noted that the Goelet *et al.* '712 published international application, which was not specifically identified in the rejection of the claims set out in the first sentence of Section 10, disclosed genetic bit analysis methods. It was asserted in the Office Action that it would have been *prima facie* obvious to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication, which was also not specifically identified in the rejection of the claims set out in the first sentence of Section 10, with the use of the genetic bit analysis or allele specific amplification to develop the data, in view of a statement in the Goelet *et al.* published application on page 8, lines 27 through 33. It was asserted that an ordinary practitioner would have been motivated to substitute the genetic bit analysis method for PCR amplification in order to minimize the need for gel electrophoresis and enhance the automatability of the process to speed analysis and minimize costs as assertedly motivated by the Goelet *et al.* '712 published international application.

C. Summary of the Present Amendments
And Request for Reconsideration

In the present response, claims 51 through 54 inclusive, claims 56 through 74 inclusive, 77, 83, 84, 88 through 90 inclusive, 99, 101, and 103 through 105 inclusive have been cancelled without prejudice.

Claims 79, 85 through 87 inclusive, 94, 96, 97, 100, and 102 have been amended.

New claims 106 through 115 inclusive have been added to the present response. The new claim 96 finds support in the application as originally filed, for example, at page 2, lines 6 through 20; page 9, line 23 through page 10, line 1; and page 15, lines 1 through 12. New

claim 107 finds support, for example, at page 9, lines 3 through 8 and page 17, lines 11 through 16. New claim 108 is supported at page 15, lines 1 through 12, for example. New claim 109 is supported, for example, at page 19, lines 3 through 25. New claim 110 finds support, for example, at page 4, lines 1 through 27. New claim 111 is supported, for example, at page 17, lines 23 through 26. New claim 112 finds support, for example, at page 14, lines 10 through 13 and page 17, lines 1 through 10. New claim 113 is supported at page 8, lines 8 through 18, for example. New claims 114 and 115 find support, for example at page 5, lines 12 through 16. It is submitted that none of new claims 106 through 115 inclusive constitutes new matter.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejections Under 35 U.S.C. § 112, First and Second Paragraphs

Although it is submitted that the expression "genotypic-class identifier" cited in the Office Action of 18 December 2003 in connection with the rejection of claims 96 through 105 inclusive under 35 U.S.C. § 112, first paragraph and the rejection of those claims under 35 U.S.C. § 112, second paragraph would have been completely clear and definite to a person of ordinary skill in the art as of the effective filing date of the subject application with the subject application at hand and moreover that the expression found ample support in the application as filed, claims 96 and 97 have been amended above to substitute --genotypic class-- for "genotypic-class identifier." Consequently it is submitted that claims 96 through 105 inclusive particularly as amended meet the standards of 35 U.S.C. § 112, first and second paragraphs, and that the rejection of claims 96 through 105 inclusive under 35 U.S.C. § 112, first and second paragraphs, should therefore be withdrawn.

E. The Rejection Under 35 U.S.C. § 102(b)

Claims 51 through 54 inclusive and 69 through 74 inclusive have been cancelled without prejudice in the present reply and therefore the final rejection of such claims under 35 U.S.C. § 102(b) as unpatentable over the Kimpton *et al.* publication has been obviated. It is submitted that the method of each of the pending claims 75, 76, 78 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, 100, 102, and 106 through 115 inclusive as amended is neither disclosed by nor obvious in view of the Kimpton *et al.* publication.

F. The Rejections Under 35 U.S.C. § 103

F.1 The Kimpton *et al.* Publication in View of the Clark Publication Variously Further in View of the Goelet *et al.* '712 Published Application and the Backman *et al.* '663 Patent

As noted above, claims 51 through 54 inclusive and 56 through 74 inclusive have been cancelled without prejudice in the present reply after final action. Consequently, the final rejections under 35 USC § 103(a) in the outstanding Office Action of claims 51 through 54 inclusive and 60 through 74 inclusive as unpatentable over the Kimpton *et al.* publication in view of the Clark publication; of claims 51 through 54 inclusive and 56 through 74 inclusive as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of the Goelet *et al.* '712 published international application; and of claims 51 through 54 inclusive, 56, 58, and 60 through 74 inclusive as unpatentable under the Kimpton *et al.* publication in view of the Clark publication and further in view of the Backman *et al.* '663 patent have been rendered moot.

F.2 The Kimpton *et al.* Publication in View of the Ledwina *et al.* Publication as Motivated in View of the Jeanpierre Publication

At the outset, we note that it was admitted in the next-to-last paragraph on page 9 of the Office Action of 18 December 2003 that the Kimpton *et al.* publication, the principal citation relied on in the Office Action, did not disclose establishing a distribution set of probability distributions. The Kimpton *et al.* publication did not therefore disclose determining a measure of a conditional probability of each genotype of interest at a locus by applying reaction values to the distribution, as seemingly also admitted in the next-to-last paragraph on page 9 of the Office Action. The attorneys for the applicants fully agree with the analysis of the Kimpton *et al.* publication in the paragraph under discussion on page 9 of the Office Action to the effect that the Kimpton *et al.* publication does not disclose the establishment of a distribution set of probability distributions and submit in addition that the Ledwina *et al.* publication does not cure the admitted infirmities of the Kimpton *et al.* publication as a reference against presently pending claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, and 96 through 98 inclusive as amended, for the reasons discussed below.

The Kimpton *et al.* publication disclosed automated DNA profiling, based on detection of amplified tri-, tetra-, and pentanucleotide short-tandem-repeat ("STR") loci by electrophoresis on denaturing polyacrylamide sequencing gels using automated fluorescence-based technology. According to the abstract of the Kimpton *et al.* publication, the system of the publication used an internal size standard in each sample to permit the short-tandem-repeat products amplified by PCR to be sized automatically. According to page 13, column 3, lines 13 through 19, the ability to resolve PCR products differing in size by just one base allowed precise allele designation. Three multiplex short-tandem-repeat systems containing a total of fourteen different loci were used, with different fluorescent markers used for loci which had overlapping allele size ranges.

Concerning the technique for automatically sizing the short tandem repeat products in the procedure of the Kimpton *et al.* publication, the publication disclosed at page 16, column 1, lines 9 through 18 that amplification products of the short-tandem-repeat loci were tagged by the attachment of a fluorescent dye molecule to one of each pair of the locus-specific amplification primers. Amplification products from each of the three multiplex amplification-reaction systems, each together with a dye-labeled internal lane standard, were respectively electrophoresed for eight hours on a polyacrylamide denaturing sequencing gel in an automated DNA sequencer. See page 15, column 1, lines 17 through 25 of the publication. During electrophoresis on the denaturing polyacrylamide gels, amplified products were detected by laser scanning. According to column 1, lines 17 through 34 of page 15 of the Kimpton *et al.* publication, fragment sizes after electrophoresis on the automated DNA sequencer were determined using software employing a method of second order regression to establish a curve of best fit for the internal standard in each lane. According to column 3, lines 42 through 46 of page 19 of the publication, the software sized PCR products automatically against the internal ladder standard. It was disclosed at page 16, column 1, line 51 through column 2, line 15 of the Kimpton *et al.* publication that for twelve of the fourteen short-tandem-repeat loci, the maximum band-size range was sufficiently small relative to the minimum repeat-unit size to permit unambiguous allele designation. For the remaining two loci, according to page 16, column 2, line 16 through column 3, line 14 and page 19, column 3, line 56 through page 20, column 1, line 4 of the publication, variability between gels did not allow reliable allele designation and it was necessary to run an allelic ladder on each gel for the two loci in question. Other than the reference to second order regression, internal operation of the software for determining fragment sizes against an internal lane standard does not appear to be described in the Kimpton *et al.* publication. As noted above, the attorneys for the applicants agree with the assessment in the next-to-last paragraph on page 9 of the Office Action of 18 December 2003 that the Kimpton *et al.*

publication did not disclose establishing a distribution set of probability distributions and applying a reaction value to the distributions to determine a measure of a conditional probability of each genotype of interest at the genetic locus under investigation.

In contrast, independent claim 75 of the subject application is directed to a method for determining the genotype at a genetic locus for a sample of genetic material obtained from a biological sample which includes a step, among others, of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of claim 75 further includes a step of applying a first reaction value indicative of the presence of a given allele at the locus to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. The method of claim 75 also includes a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution.

Independent claim 96 of the subject application as amended is directed to a method of associating with a sample of genetic material one of a predetermined plurality of genotypic classes defined with respect to a genetic locus sited in the genetic material together with a corresponding confidence measure, which includes a step of obtaining with respect to each of the genotypic classes corresponding reaction-value data-point conditional-probability-measure distribution information, which provides, over a set of hypothetical reaction-value data points, a conditional probability measure as a function of the reaction values of each hypothetical reaction-value data point given the genotypic class. The method of amended claim 96 includes the further step of evaluating for each of the genotypic classes the corresponding reaction-value data-point conditional-probability-measure distribution information with respect allele-indicative reaction values of the reaction-value data point corresponding to the

sample, to obtain for each of the corresponding genotypic classes a reaction-value data-point conditional probability measure of the reaction-value data point, given the genotypic class.

The Ledwina *et al.* publication disclosed a statistical method for analyzing the allelic assignments for a population of multiallelic diploid individuals to determine whether the population exhibits so-called Hardy-Weinberg equilibrium. The statistical method for determining whether a population exhibits Hardy-Weinberg equilibrium takes as input data the allelic assignments for the population. The method of the Ledwina *et al.* publication involves processing previously determined allelic assignments from the individuals of a population. In contrast, the method of the Kimpton *et al.* publication involves determining certain allelic assignments for an individual based on analyzing a sample of DNA taken from the individual. It is submitted that the Ledwina *et al.* publication in no way cures the infirmities of the Kimpton *et al.* publication as a reference against claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, and 96 through 98 inclusive of the subject application as amended.

The Jeanpierre publication disclosed a method for deriving the probability for a genotype of an "unsampled" person based on genotype assignments of family members in the pedigree of the unsampled person. The Kimpton *et al.* publication disclosed a method for determining certain allelic assignments for an individual based on detecting certain short tandem repeats in a sample of DNA taken from the individual.

Each of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication is concerned with a different and disparate sort of genetic analysis: determination of a DNA profile of an individual from a sample of the individual's DNA in the case of the Kimpton *et al.* publication, whether a population of multiallelic diploid individuals whose allelic assignments have previously been determined exhibits a Hardy-Weinberg equilibrium state in the case of the Ledwina *et al.* publication, and evaluation of the

probability of the genotype of an individual whose genetic material is not available for testing from the genotypes of family members in the pedigree of the individual in the case of the Jeanpierre publication. It is submitted that in view of the fundamentally different sorts of genetic analysis disclosed in the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication, it would never have occurred to a person of ordinary skill in the art as of the effective filing date of the subject application to combine these three publications as proposed in the outstanding Office Action, and that, had such a hypothetical combination occurred to such a person, the combination would not have suggested the subject matter of claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, and 96 through 98 inclusive of the subject application as amended.

It is submitted therefore that the Kimpton *et al.* publication considered alone or in any combination with the Ledwina *et al.* publication or the Jeanpierre publication would not have disclosed or suggested the method of any of presently pending claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, and 96 through 98 inclusive of the subject application as amended to a person of ordinary skill in the art, as of the effective filing date of the application. The final rejection of claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, and 96 through 98 inclusive as amended in the outstanding Office Action as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication as motivated in view of the Jeanpierre publication, it is submitted therefore, was without justification and should be withdrawn.

F.3 The Kimpton *et al.* Publication in View of the Ledwina *et al.* Publication as Motivated in View of the Jeanpierre Publication and Further in View of the Clark Publication

We note at the outset that the Clark publication was not specifically cited against any claims in connection with the final rejection under 35 U.S.C. § 103(a) set forth in the first sentence of Section 9 of the Office Action of 18 December 2003, although the publication was

discussed in Section 9 as if the publication had been combined with the hypothetical combination of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication set out in the preceding Section 8. In view of the discussion of the Clark publication in Section 9, we will treat the final rejection of Section 9 as if it included the publication.

The Clark publication disclosed a method for resolving ambiguities in sequencing on sequencing gels alleles from PCR-amplified DNA samples from diploid individuals. The method of the Clark publication involved obtaining DNA samples from a population of diploid individuals and identifying a homozygote or a single heterozygous site on a sequencing gel. According to lines 2 through 6 on page 112 of the Clark publication, a homozygote could be recognized on a sequencing gel by a lack of ambiguous sites. Each time a homozygote was found, a haplotype had been identified. Two haplotypes were identified if the individual had a single heterozygous site. The method of the Clark publication involved tallying the haplotypes identified by finding homozygotes and single heterozygous sites. As disclosed at line 7 through 12 on page 112 of the Clark publication, the method of resolving ambiguous sequences entailed determining, for each known haplotype, whether the haplotype could be made from some combination of an ambiguous site. For each such haplotype, the complement of the haplotype was recovered as another potential haplotype. The process was continued until all haplotypes had been recovered or no new haplotype could be found.

The Clark publication in no way connects the disparate methodologies of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication. For the reasons discussed in the preceding subsection, it is submitted that it never would have occurred to a person of ordinary skill in the art to combine the disparate methods of the Kimpton *et al.* publication and the Ledwina *et al.* publication, with or without the motivation of the Jeanpierre publication, in any combination with each other or with the Clark publication

as of the effective filing date of the subject application, and that had such a hypothetical combination occurred to such a person, the combination would not have suggested the method of presently pending claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, and 96 through 98 inclusive of the subject application as amended. It is submitted that the final rejection of claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, and 96 through 98 inclusive as amended under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication, in view of the Ledwina *et al.* publication, as motivated in view of the Jeanpierre publication, and further in view of the Clark publication was without justification and should be withdrawn.

F.4 The Kimpton *et al.* Publication in View of the Ledwina *et al.* Publication as Motivated in View of the Jeanpierre Publication and Further in View of the Goelet *et al.* '712 Published International Application

At the outset we note that the Goelet *et al.* '712 published international application was not specifically cited against any claims in connection with the final rejection under 35 U.S.C. § 103(a) set forth in the first sentence of Section 10 of the Office Action of 18 December 2003, although the published application was discussed in Section 10 as if the publication had been combined with the hypothetical combination of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication set out in the earlier Section 8. In view of the discussion of the Goelet *et al.* '712 published international application in Section 10, we will treat the final rejection of Section 10 as if it included the published application.

As disclosed in the abstract, the Goelet *et al.* '712 published international application disclosed a method for determining the identity of a nucleotide base at a specific position in a nucleic acid of interest and a method for determining the presence or absence of a particular nucleotide sequence in a sample of nucleic acids. The methods entailed contacting nucleic acid of interest with an oligonucleotide primer under hybridizing conditions and treating the

resulting duplex, if any, with a terminator reagent under conditions permitting base pairing of a complementary terminator present in the reagent and the occurrence of a template-dependent, primer extension reaction so as to incorporate the terminator at the 3' end of the primer. The identity of the terminator at the 3' end of the primer determined whether the hybridization occurred and the identity of the base complementary to the terminator.

The Kimpton *et al.* publication disclosed an automated DNA profiling method which employed three multiplex groups of particular three to five-base pair short-tandem-repeat loci which were amplified groupwise by PCR and analyzed by denaturing polyacrylamide sequencing gels.

The Goelet *et al.* published application does not connect the disparate methodologies of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication. For the reasons discussed in the earlier subsection F.2, it is submitted that it never would have occurred to a person of ordinary skill in the art, as of the effective filing date of the subject application, to combine the disparate methods of the Kimpton *et al.* publication and the Ledwina *et al.* publication, with or without the motivation of the Jeanpierre publication, in any combination with each other or with the Goelet *et al.* published application, and that had such a hypothetical combination occurred to such a person, the combination would not have suggested the method of presently pending claims 75, 76, 78 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, and 100 of the subject application as amended. It is submitted that the final rejection of claims 75, 76, 78 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, and 100 under 35 U.S.C. § 103(a) is unpatentable over the Kimpton *et al.* publication, in view of the Ledwina *et al.* publication, as motivated in view of the Jeanpierre publication, and further in view of the Goelet *et al.* '712 published international application was unwarranted and should be withdrawn.

G. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended meet the standards of 35 U.S.C. § 112, first and second paragraphs, and are patentable over the art of record considered alone or in any combination. Withdrawal of the outstanding final rejection and allowance of the application is therefore earnestly solicited.

Respectfully submitted,

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